

Bilateral testicular metastasis from prostatic adenocarcinoma mimicking an intertubular pattern of seminoma and expressing Rhamm

ABSTRACT

Adenocarcinoma of prostate metastasizing to testis is a rare occurrence and is incidentally detected in orchiectomy specimens. The pattern of metastasis may mimic a primary neoplasm of testis like a seminoma or lymphoma and pose a diagnostic difficulty for the pathologist. A rare case of bilateral testicular metastasis of prostatic adenocarcinoma is presented wherein the metastatic cells expressed CD168, a receptor for hyaluronan mediated motility (Rhamm), implicated in the development of androgen independence in prostate cancer.

KEY WORDS: CD168, metastasis, prostatic adenocarcinoma, testis

INTRODUCTION

Prostatic adenocarcinoma is one of the commonest malignancies afflicting the adult male population. The favored sites of metastasis of prostatic cancer are the bone, liver and lungs.^[1] Prostatic adenocarcinoma rarely metastasizes to testis and is incidentally detected in orchiectomy specimens performed for hormonal deprivation therapy with an incidence rate of about 2-4%.^[2] Metastases are usually unilateral, however, bilateral metastases are also documented.^[3,4] For the pathologist the diagnosis of testicular metastasis of prostatic adenocarcinoma can be challenging as it can mimic primary testicular malignancies like lymphoma and seminoma with intratubular, intertubular and nodular pattern of involvement of testicular parenchyma.^[5] The mode of spread to testis is via lymphatics in majority of the cases.^[6] CD 168 or Rhamm is a receptor for hyaluronan mediated motility and has been recently implicated in the evolution of androgen independent prostate cancer and metastasis in human bone marrow endothelium.^[7,8] We report an unusual case of testicular metastasis of a prostatic adenocarcinoma with prominent seminoma like nucleoli, intertubular infiltrative pattern and focal expression of CD168.

CASE REPORT

A 56-year-old male presented to the Urologic

Oncology department of our tertiary Cancer Center with history of backache and difficulty in micturition since six months. The serum prostate specific antigen (PSA) at presentation was 173.433 ng / ml and serum alkaline phosphatase level was 4960 U / L. Digital rectal examination revealed a hard prostate but rectal mucosa was free.

The trans-rectal ultrasound (TRUS)-guided core biopsies from right and left prostate lobes were performed which on pathological evaluation were compatible with a diagnosis of prostatic adenocarcinoma, Gleason's score 7. On Tc-99m MDP bone scan osteoblastic metastasis were seen involving skull, ribs, upper half of humerus, vertebrae, bilateral sacroiliac joint and trochanter of femur. The option of orchiectomy was refused by the patient and so he was prescribed gonadotropin-releasing hormone (GnRH) analogue leuprolide. However, following the initial good response to GnRH analogues, within 10 months the patient developed progressive symptoms of bone pain and the PSA level rose to 649.648 ng / ml. A bilateral therapeutic scrotal orchiectomy was performed to reinforce the androgen blockade.

Pathological features

Grossly, both the testes were of normal size for age. On cut sections, each testis had a firm gray white nodular area near one pole measuring about 1x 0.5 cm. The epididymis, vas deferens and cord cut margins were unremarkable.

Santosh Menon,
Sumeet Gujral,
Ganesh Bakshi¹,
Hemant B. Tongaonkar¹

Departments of Pathology,
and ¹Urologic Surgical
Oncology, Tata Memorial
Hospital, Parel, Mumbai-
400 012, India

For correspondence:

Dr. Santosh Menon,
Department of Pathology,
Tata Memorial Hospital,
Parel, Mumbai - 400 012,
India.
E-mail: santosh.menon@
rediffmail.com

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On microscopy, within the nodular areas, malignant cells were seen in the interstitium in small nests and groups among the seminiferous tubules [Figure 1]. These cells were round to oval, had prominent nucleoli and moderate cytoplasm [Figure 1 inset]. At some foci, the tumor cells invaded the fibro sclerotic seminiferous tubules. The adjacent tubules were atrophic and comprised predominantly of sertoli cells. Lymphatic tumor emboli were noted prominently beyond the region of the nodular deposit. In addition to a metastatic prostatic carcinoma, a differential diagnosis of seminoma was entertained on morphology due to the striking nucleolar prominence. On immunohistochemistry, the tumor cells were highlighted by PSA and were non-reactive with c-kit, cytokeratin or placental alkaline phosphatase (PLAP), thereby confirming the prostatic origin of the metastatic deposit [Figure 2]. Interestingly, a few of the tumor cells were marked with Rhamm (CD168) immunostain [Figure 3].

DISCUSSION

Testis is a rare site for involvement by secondary malignancies with the reported incidence being about 0.06-2.5% as seen at autopsy or as an incidental finding after therapeutic orchiectomy.^[1,2,9] The testicular microenvironment is not conducive to the establishment and growth of secondary tumors owing to relatively low temperature of scrotum.^[10] The most common tumors metastasizing to testis included lung, melanoma, prostate and kidney.^[1,2] However, in recent studies, prostate cancer has been the commonest primary site.^[5,6] This increased detection may be related to the therapeutic orchiectomies these patient undergo. In the present case also the metastasis was an incidental finding observed at orchiectomy done for androgen ablation. The interesting feature was the bilateral involvement which is exceptionally rare, unilateral metastasis being the more common occurrence.^[4]

Metastatic tumors to testis may have an intratubular, intertubular or an intrarete infiltrative pattern and need to be distinguished from seminoma and rete testis carcinoma.^[5] In our case, the intertubular pattern of infiltration and the cellular morphological features with prominence of nucleoli, abundant cytoplasm and loosely cohesive cells mimicked a seminomatous tumor which was, however, excluded by appropriate immunohistochemical markers (PSA positivity and negativity for c-kit, PLAP). Intertubular pattern is also prominent in cases of lymphomas arising in the testis.^[2]

Hyaluronan (HA) is a tumor promoter and enhancer in transformation of androgen-independent (AI) prostate cancer. CD168, a receptor for HA-mediated motility, and its downstream signal molecules, promote androgen independent rather than androgen-dependent prostate cancer and enhance cell invasion and metastasis in human bone marrow endothelial layers. The interaction of androgen and AR is essential for regulating HA-mediated cancer progression

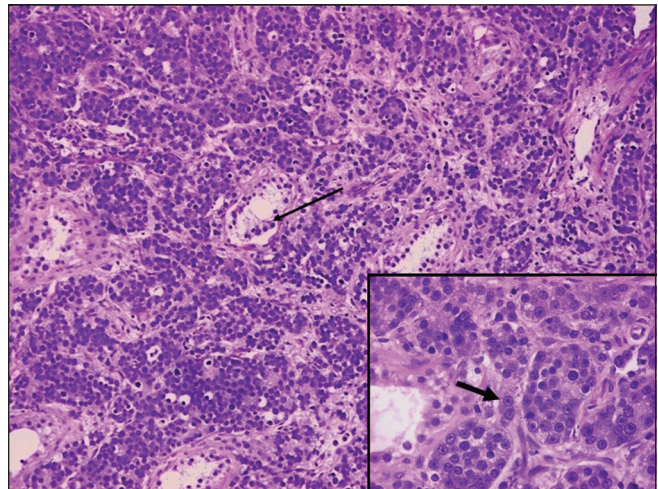


Figure 1: Section shows intertubular pattern of metastatic prostatic adenocarcinoma. Note the atrophic seminiferous tubules (thin arrow) (H and E $\times 100$). Inset: The nucleolar prominence in tumor cells mimick the morphology of a seminoma (thick arrow). (H and E, $\times 200$)

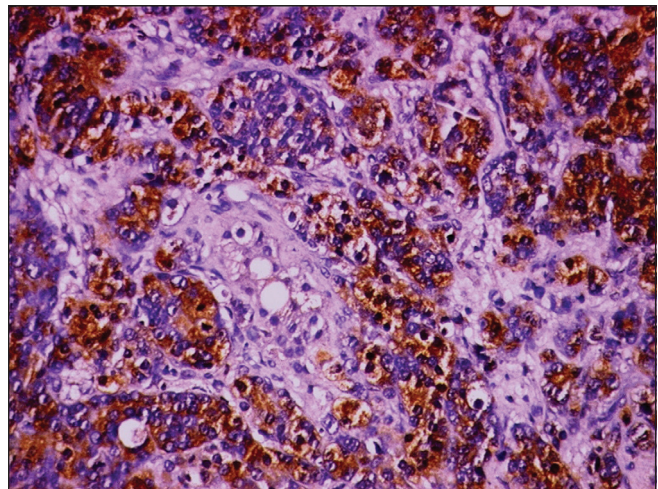


Figure 2: The tumor cells are immunopositive for prostate specific antigen (PSA). (Immunoperoxidase method, $\times 200$)

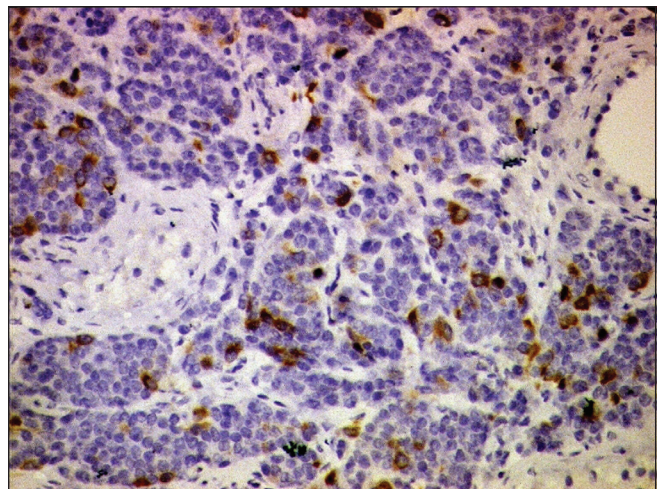


Figure 3: CD168 (Rhamm) immunostain marks some of the metastatic tumor cells. (Immunoperoxidase method, $\times 200$)

via the CD168 / ROCK signal transduction pathway and the androgen receptor dysregulation not only causes CD168 over expression but also activates HA-mediated CD168 signaling in malignant cancer progression and metastasis of hormone refractory prostate cancer.^[7,8] In our case, on retrospect, the tumor in core biopsy sample did not express CD168 whereas expression was seen in some metastatic cells in testis. It can be argued that the absence of CD168 in the core biopsy sample of carcinoma may be a sampling error as the core sample comprised of adenocarcinoma of Gleason's score 7 whereas the metastatic adenocarcinoma had a higher degree of anaplasia. Androgen deprivation may also have altered the morphological aspects at the metastatic site. It can be surmised that the more undifferentiated tumor component acquired CD168 with consequent metastatic potential due to complex interplay of androgen receptor, hyaluronan and CD 168. Also, in the present case, the androgen independence as judged by the progression of disease while on GnRH analogues further corroborates the role of CD168. The clinical implications of testicular metastasis are not well established. A study of 1693 orchiectomies in advanced prostate cancer by Korkes *et al.*^[11] concludes that testicular metastasis connotes an aggressive behavior and poor prognosis.

In conclusion, we have presented an unusual case of bilateral testicular metastasis of prostatic adenocarcinoma and have highlighted the biological implications of CD168 expression. The role of CD168 as an upfront predictive and prognostic marker in organ confined prostatic cancer needs to be further studied by application in larger series of cases.

REFERENCES

1. Saitoh H, Hida M, Shimbo T, Nakamura K, Yamagata J, Satoh T. Metastatic patterns of prostatic cancer: Correlation between sites and organ involved. *Cancer* 1984;54:3078-84.
2. Haupt B, Ro JY, Ayala AG, Zhai J. Metastatic prostatic carcinoma to testis: Histological features mimicking lymphoma. *Int J Clin Exp Pathol* 2009;2:104-7.
3. Ho CR, Ng KF, Chen JF, Wu CT, Chuang CK, Pang ST. Metastasis of prostate cancer in a single testis presented as a hydrocele: Report of a case. *Curr Urol* 2007;1:55-6.
4. Giannakopoulos X, Bai M, Grammeniatis E, Stefanou D, Agnanti N. Bilateral testicular metastasis of an adenocarcinoma of prostate. *Ann Urol (Paris)* 1994;28:274-6.
5. Ulbright TM, Young RH. Metastatic carcinoma to the testis: A clinicopathologic analysis of 26 nonincidental cases with emphasis on deceptive features. *Am J Surg Pathol* 2008;32:1683-93.
6. Patel SR, Richardson RL, Kvoles L. Metastatic cancer to the testes: A report of 20 cases and review of the literature. *J Urol* 1989;142:1003-5.
7. Lin SL, Chang D, Chiang A, Ying SY. Androgen receptor regulates CD168 expression and signaling in prostate cancer. *Carcinogenesis* 2008;29:282-90.
8. Lin SL, Chang D, Ying SY. Hyaluronan stimulates transformation of androgen-independent prostate cancer. *Carcinogenesis* 2007;28:310-20.
9. Qazi HA, Manikandan R, Foster CS, Fordham MV. Testicular metastasis from gastric carcinoma. *Urology* 2006;68:890.e7-8.
10. Smallman LA, Odedra JK. Primary carcinoma of sigmoid colon metastasizing to epididymis. *Urology* 1984;23:598-9.
11. Korkes F, Gasperini R, Korkes KL, Silva Neto DC, Castro MG. Testicular metastases: A poor prognostic factor in patients with advanced prostate cancer. *World J Urol* 2009;27:113-5.

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